REMARKS

Entry of the foregoing and favourable examination and reconsideration of the subject-application, as amended, pursuant to and consistent with 37 C.F.R. §1.112, and in the light of the Remarks which follow, are respectfully requested.

By way of response, claims 21, 30, 33, 43, 47, 48, 53, 54, 58, 64 and 65 have been amended, and claim 36 has been canceled. Some amendments are made to correct SEQ ID NOS: and/or to clarify the claimed subject-matter. New claims 66 to 69 have been added. The support for these claims is set forth below. No new matter is presented. Claims 21, 23, 30 to 34, and 40 to 69 are pending.

The support for new claims 66 to 69 is as follows :

The support for Claim 66 is at least at page 13, line 4, to page 15, line 9 of the specification.

The support for Claim 67 can be found at least at page 12, lines 7-8 of the specification, and in the former claims.

The support for claims 68 and 69 can be found throughout the specification.

Claim Rejections – 35 U.S.C. § 112, first paragraph

Claims 23, 30-32, 36, 53 and 65 were rejected under 35 U.S.C. § 112, first paragraph, because they allegedly contain subject matter which was not described in the specification in such a way as to convey to one skilled in the relevant art that the inventors had possession of the claimed invention at the time the application was filed.

This rejection is partly obviated by the amendments made to claims 21, 30, 33 and 65 and cancellation of claim 36, and is partly being traversed, for the reasons set forth below.

Regarding claims 30-32 and 65, the Examiner considered that there was no written description for the recitation "a Survival Motor Neuron disorder". Claims 30 and 65 have been amended by deleting the phrase "wherein the presence of said truncation, deletion or mutation is indicative of a Survival Motor Neuron disorder", thereby rendering the rejection of these claims moot.

Claim 53 has also been rejected for lack of written description. This claim has been amended by replacing the word "defect" by "truncation, a deletion or a mutation", and by cancelling the reference to SEQ ID No: 22, as suggested by the Examiner. The rejection of claim 53 should hence be rendered moot.

Claims 30, 36 and 65 have been rejected as allegedly lacking proper written description for using SSCP analysis with "any pair of primers contained in SEQ ID Nos : 12 or 22". The reference to SEQ ID No: 22 in claim 36 has been cancelled by amendment of the claim.

Regarding claim 30, the primers are defined as "contained in the sequence of nucleotides 921 to 1469 of SEQ ID No: 12", which is supported at least by the phrase at page 12, lines 10-11.

Claim 65 has been amended and now pertains to a method comprising a step of amplification with primers selected from SEQ ID Nos: 5 to 8. New claim 66 pertains to the same method, but wherein the primers are selected from the group of SEQ ID Nos: 24 to 57. The use of these primers for performing SSCP analysis is explicitly recited at least at page 13, paragraph 2.

Therefore, in view of the above, withdrawal of this rejection of claims 30 and 65 is respectfully requested.

Claims 21, 23, 30-34, 36, and 40-65 stand rejected under 35 USC 112, first paragraph, because the Examiner considered that the specification provides enablement only for a method of detecting specific motor disease states related to specific mutations, using structurally defined material, but not for a generic method or kit, that does not identify the specific disease state being detected and the specific material used therefor. The Examiner more specifically argues that the claims merely constitute an invitation for others to discover what pairs of primers may work to perform the invention, and therefore that undue experimentation is required to discover how to make and use Applicants' invention. This rejection is partly obviated by amendment of claims 21 and 30 and cancellation of claim 36, and is traversed in part.

Claims 21 and 30 have been amended to recite that the set of primers is suitable for amplification of a fragment of the sequence of nucleotides 921 to 1469 of SEQ ID No: 12. Applicants respectfully submit that the skilled artisan perfectly knew how to chose primers in a defined sequence to amplify part of it, as described for example in Sambrook et al, 1989, copy of which is enclosed. Rather than the identification of a couple of primers enabling the amplification of part of the SMN gene, the Examiner's rejection seems to be based on the fact that defining the primers only by their location in part of the SMN gene does not assure that the amplified fragment will comprise a polymorphism indicative of a specific disease. However, Applicants submit that the true teaching of the present invention is the identification of the SMN gene, a pioneering invention which was previously unknown. Moreover, Applicants have demonstrated that the SMN gene can be truncated or even lacking in SMA patients, as mentioned for example at page 28, second and third full paragraphs. Hence, a great number of couples of primers can be used to amplify part of the SMN gene, and thereby perform the method of the invention.

This identification of the primers can be done by the skilled artisan without undue experimentation due to the identification of the SMN gene and of its differences having regard to the C-BCD541 sequence. It should be recalled again at this point that the ultimate question in an enablement issue is whether or not the specification contains a sufficiently explicit disclosure to enable one skilled in the art to produce the invention without exercise of undue experimentation, bearing in mind the teachings of the description and the level of skill in the art at the time the invention was filed. At the time the present invention was filed it was routine practice for the skilled artisan to make primers based on the entire nucleotide sequence of the SMN gene disclosed in SEQ ID No. 22 in the present invention. The synthesis of oligonucleotides was well established prior to the filing of the present invention and with the sequence in hand, primers could be easily obtained.

As stated in *Ex parte D*, 27 USPQ2d1067, 1069-170 (Bd. Pat. App. & Int'f 1993):

> Parallel to the holding in the *Wands* decision, there was a high level of skill in this art at the time the application was filed and the methods needed to practice the invention were well known...[R]outine experimentation may involve rather extensive studies without straying from "undue" experimentation.

Thus, the present invention fulfills the criteria of *Ex Parte D, supra*, in which an enablement rejection was not maintained.

Moreover, the Examiner states that there is lack of enablement for any primers since "For example, any random primer within a given sequence coding in the same direction would give rise to only a single strand, and therefore, make it impossible to amplifying a given polymorphism, etc. because both strands must be present to accomplish such, if known and defined" (pages 5-6 of the o.a.).

However, a person skilled in the art is very capable of choosing primers that work, which are, by definition, on the two DNA strands. Applicants submit that the PTO Board of Appeal have recognized that inoperative embodiments in a claim would be recognized by the skilled artisan and that the skilled artisan would find no benefit in seeking out embodiments that do not work. This is clear from the teachings of *Ex parte Cole*, 223 USPQ 94, 95-96 (PTO bd. App. 1983), wherein the Board stated the following :

> Claims are addressed to the person of average skill in the particular art. Compliance with 112 must be adjudged from that perspective, not in a vacuum. It is always possible to theorize some combination of circumstances which would render a claimed composition or method inoperative, but the art-skilled would assuredly not chose such a combination.

Thus, the Examiner's reasoning for maintaining this rejection is unreasonable and cannot be sustained.

Applicants respectfully submit that the skilled artisan, reading the specification, can perfectly understand the implication of the SMN gene, and provide a pair of primers with which part of it will be amplified for diagnosis purpose.

Finally, Applicants respectfully submit that specific sequence identification numbers are recited in claims 40-65, and that the Examiner has not indicated why these claims are being rejected as not being enabled by the specification. Therefore, and in view of the above, Applicants respectfully submit that the specification enables the skilled artisan to perform the method and kits of claims 21, 23, 30-34, and 40-65 as amended.

Withdrawal of this rejection is hence respectfully requested.

Claims Rejections – 35 U.S.C. § 112, second paragraph

Claims 30-31, 36, 48 and 65 have been rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite and incomplete because the Examiner considers that the SSCP conditions should be completely recited in the claims, and that the term "analysis" is unclear in the phrase "SSCP analysis". This rejection is obviated by amendment to the claims.

Claim 36 has been cancelled. Claim 30 has been amended by adding that the primers are suitable for amplification of a fragment of defined sequences, thereby clarifying the definition of said primers.

Claims 30, 48 and 65 have further been amended by reciting that SSCP analysis comprises comparing a pattern of DNA fragments obtained from the patient sample to a pattern of DNA fragments obtained from a control sample. Moreover, Applicants submit that the claims are to be read in light of the specification, and that the conditions for performing SSCP are described, for example, in Example 10, pages 44-45 of the specification. It is also very clear from the specification that a "SSCP" analysis consists in comparing the SSCP pattern of a sample to be tested to that of a control which comes from a healthy individual. Such comparisons between samples from patients and samples from healthy controls are indeed described at least at pages 28 to 30 of the specification.

From the above, withdrawal of the rejection is respectfully requested.

Claims 30 to 33, 36 and 65 were rejected under 35 U.S.C. § 112, second paragraph, as being incomplete for omitting essential steps. This rejection is obviated by amendment to claims 30, 33 and 65 and cancellation of claim 36.

Indeed, claims 30 and 65 have been amended by cancellation of the phrase "wherein the presence of said truncation, deletion or mutation is indicative of a Survival Motor Neuron disorder", and the last step of these methods is now the detection of the presence or absence of an alteration in the SMN gene. Claim 33 has also been amended by reciting that theabsence of detectable hybrids is indicative of the presence of Spinal Muscular Atrophy.

As regards claims 31 and 33, Applicants respectfully submit that the inventors have clearly demonstrated a strong correlation between an alteration in the SMN gene and Spinal Muscular Atrophy, as described, for example, at pages 28 to 31 of the specification. As indicated at least at page 28, last paragraph, the SMN gene is absent or truncated in 98% of the SMA patients (and 0% of healthy controls). When present, the inventors have shown that it exhibits transcriptional differences having regard to the controls, as concluded at least at page 31, second paragraph. Therefore, Applicants respectfully submit that the meaning of claims 31 and 33 is clear : a difference between the SMN gene of a tested sample and that of controls from healthy individuals is indicative of SMA, whereas the absence of such a difference is indicative of the absence of SMA.

Therefore, withdrawal of this rejection is respectfully requested.

Claims 23, 33-34 and 53 have been rejected under 35 U.S.C. § 112, second paragraph, because the "stringent hybridization conditions" were allegedly not sufficiently defined. This rejection is obviated by claim amendment. As already mentioned at page 12 of the response filed on February 13, 2002, this rejection is irrelevant concerning claim 23, since this claim does not recite stringent conditions. Specific hybridization conditions have been added to claims 33 and 53. The support for these amendments is at least in Example 6 of the specification.

Therefore, this rejection should be rendered moot.

Claims 43, 47-48 and 64 have been rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. This rejection is obviated in part and is being traversed in part.

Claims 43 and 64 have been amended by reciting that the amplification is performed by PCR. Claim 47 has been amended by specifying that the restriction cleavage is performed using the *Bsr*-1 enzyme (as supported at least by former claim 32), or the *Hind*III, *Sac*I or *Kpn*I restriction enzymes, as supported at least by the last paragraph of page 23 and the first one of page 24. Claims 43 and 47 have been further amended by reciting that the PCR amplification and the restriction, respectively, are performed prior to the analysis of exons 7 or 8.

Concerning Claim 48, Applicants respectfully disagree with Examiner's rejection. Indeed, Applicants consider that "subjecting said patient T-BCD541 gene to single strand conformation polymorphism analysis" clearly designates having the denatured amplified DNA migrate on a gel, together with a control sample coming from a healthy individual, comparing the band shifts, and deducing whether the patient SMN gene is defective. This appears clearly from the specification, for example, from the paragraph bridging pages 32 an 33 and Example 10.

In view of the above, withdrawal of the rejection is respectfully requested.

Claims Rejections – 35 U.S.C. § 102 (b)

Claims 53 and 23 have been rejected under 35 U.S.C 102(b) as being anticipated by Stratagene Cloning Systems Catalog (1994). More precisely, the Examiner considered that purified random 9-mer oligonucleotide primers/probes would inherently hybridize to SEQ ID Nos : 1, 2, 10-13 or 22, and therefore that the kits sold by Stratagene under # 300385 anticipate the claimed subject-matter. This rejection is respectfully traversed.

The Stratagene Cloning Systems Catalog (1994) provides a system to generate probes and is not linked to any specific DNA sequence in which probes can be generated. Moreover, this reference provides no specific sequence.

Applicants submit that it appears that the Examiner is maintaining this novelty rejection based on inherency that by mere chance, one might obtain a probe of at least 9 nucleotide sequences within SEQ ID Nos. 12 or 13 or those sequences which hybridize to SEQ ID Nos. 1, 2 or 10 to 13.

However, it is well established in the case law that inherency cannot be established for novelty purposes on the basis of mere probabilities. As stated in *Ethyl Molded Products Co. v. Betts Package Inc.*, 9 USPQ2d 1001, 1032-33 (E.D. Ky. 1988):

> The doctrine of inherency is available only when the prior inherent event can be established as a certainty. That an event may result from a given set of circumstances is not sufficient to establish anticipation, Probabilities are not sufficient...A prior inherent event cannot be based on speculation or where doubt exists.

In this present rejection, the Examiner clearly basis this rejection on cited prior art (an event) in which a multitude of doubt exists. Therefore, this rejection cannot be maintained, since it is inconsistent with the established case law.

Accordingly, withdrawal of the rejection is requested.

From the foregoing, favourable action in the form of a Notice of Allowance is respectfully requested and such action is earnestly solicited.

Pursuant to 37 C.F.R. §§ 1.17 and 1.136(a), Applicant(s) respectfully petition(s) for a three (3) month extension of time for filing a reply in connection with the present application, and the required fee of $930.00 is attached hereto.

If necessary, the Commissioner is hereby authorized in this, concurrent, and further replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. § 1.16 or under 37 C.F.R. § 1.17; particularly, extension of time fees.

Respectfully submitted,

BIRCH, STEWART, KOLASCH & BIRCH, LLP

By _____
Marc S. Weiner, #32,181
MaryAnne Armstrong, Ph.D., #40,069

P.O. Box 747
Falls Church, VA 22040-0747
(703) 205-8000

MSW/MAA/csm
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Attachment: Version Showing Marked-up Claims

VERSION SHOWING MARKED-UP CLAIMS

Claim 36 has been canceled.

Claims 21, 30, 33, 43, 47, 48, 53, 54, 58, 64 and 65 have been amended as follows:

21. (Three times amended) A kit for the *in vitro* detection of a truncation, a deletion or a mutation in the survival motor neuron gene, comprising:

a set of primers wherein said primers are contained within the sequence of nucleotides 921 to 1469 of SEQ ID NO: 12 and are suitable for amplification of a fragment of said sequence;

reagents for amplifying DNA with said primers; and

a probe for the detection of the amplified product.

30. (Three times amended) A method for detecting the presence or absence of a truncation, a deletion or a mutation in the Survival Motor Neuron gene in a DNA sample, said method comprising:

~~(a)extracting DNA from a patient sample;~~

~~(b)~~(d) amplifying said DNA in the sample with primers, wherein said primers are contained in the sequence of nucleotides 921 to 1469 of SEQ ID NO: 12 and are suitable for amplification of a fragment of said sequence;

~~(c)~~(e) subjecting said amplified DNA to a Single-Strand Conformation Polymorphism (SSCP) analysis, wherein the analysis comprises comparing a pattern of DNA fragments obtained from the patient sample to a pattern of DNA fragments obtained from a control sample to detect alterations in the patient gene; and

~~(d)~~(f) detecting the presence or absence of said truncation, deletion or mutation in the Survival Motor Neuron gene~~, wherein the presence of said truncation, deletion or mutation is indicative of a Survival Motor Neuron disorder~~.

33. (Twice amended) A method for detecting the presence or absence of Spinal Muscular Atrophy in an individual, said method comprising :

~~(a)extracting DNA from a patient sample;~~

~~(b)~~(c) hybridizing ~~said DNA~~ a DNA sample obtained from the individual with a DNA probe comprising all or part of the DNA sequence of SEQ ID NOS: 12 or 13 under ~~stringent~~ conditions having the stringency of 10% Dextran Sulphate Sodium, 1M NaCl, 0.05M Tris-HCl pH 7.5, 0.005M EDTA and 1% SDS at 65°C ;

~~(c)~~(d) detecting the hybrids formed, wherein the absence of detectable hybrids is indicative of the presence of Spinal Muscular Atrophy in the individual.~~; and~~

~~(d)detecting the presence or absence of Spinal Muscular Atrophy.~~

~~(d)~~

43. (Twice amended) The method of claim 40, wherein ~~said analyzing includes amplifying~~ all or part of the T-BCD541 gene is subjected to PCR amplification prior to analyzing the gene for alterations in exon 7 or 8.

47. (Once amended) The method of claim 40, wherein said analyzing comprises subjecting said patient T-BCD541 gene to restriction cleavage with *Bsr*I, *Hind*III, *Sac*I or *Kpn*I prior to analyzing the gene for alterations in exon 7 or 8.

48. (Once amended) The method of claim 40, wherein said analyzing comprises subjecting said patient T-BCD541 gene present in said biological sample to single strand conformation polymorphism analysis, wherein the analysis comprises comparing a pattern of DNA fragments obtained from the patient sample to a pattern of DNA fragments obtained from a control sample to detect alterations in the patient gene.

53. (Twice amended) A kit for the *in vitro* detection of a ~~defect~~ truncation, a deletion or a mutation in the Survival Motor Neuron gene, wherein said kit comprises a probe which comprises at least 9 nucleotides within a sequence of SEQ ID NO: ~~22~~ 12 or 13 or hybridizes with a sequence of SEQ ID NOS: 1, 2, or 10-13 under ~~stringent~~ conditions having the stringency of 10% Dextran Sulphate Sodium, 1M NaCl, 0.05M Tris-HCl pH 7.5, 0.005M EDTA and 1% SDS at 65°C ~~with a sequence of SEQ ID Nos: 1, 2, 10-13, or 22~~.

54. (Twice amended) A method of identifying the presence or absence of a mutation in the Survival Motor Neuron (SMN) gene in a ~~subject~~nucleic acid sample, comprising

~~(a)isolating a nucleic acid from the subject;~~

~~(b)~~(c) subjecting the nucleic acid in the sample to digestion by a restriction endonuclease, wherein restriction fragments resulting from said digestion of a mutated SMN gene differ from those obtained from a T-BCD541 gene of SEQ ID NO:22; and

~~(c)~~(d) identifying the presence or absence of a mutation in the SMN gene in the subject.

58. (Twice amended) A method of identifying the presence of Spinal Muscular Atrophy (SMA) in a subject, said method comprising:

~~(a)isolating a nucleic acid from a subject; and~~

(b) identifying a mutation in a T-BCD541 gene (SEQ ID NO: 22) in a DNA sample obtained from said subject;

wherein the presence of a mutation in the T-BCD541 gene is indicative of the presence of SMA in said subject.

64. (Twice amended) A kit for the *in vitro* detection of a defect in the ~~survival motor neuron~~ Survival Motor Neuron gene, comprising:

a set of primers wherein said primers comprise a sequence selected from SEQ ID NOS: 5 to 8 and 24 to 57;

PCR reagents for amplifying DNA with said primers; and

a probe for the detection of the amplified product.

65. (Twice amended) A method for detecting the presence or absence of a ~~defect~~ truncation, a deletion or a mutation in the Survival Motor Neuron gene, wherein the gene is present in a DNA sample obtained from an individual, said method comprising :

~~(a)extracting DNA from a patient sample;~~

~~(b)~~(d) amplifying said DNA with primers, wherein said primers ~~comprise~~ are selected from the group of ~~a sequence selected from~~ SEQ ID Nos: 5 to 8 ~~and 24 to 57~~;

~~(c)~~(e) subjecting said amplified DNA to a Single-Strand Conformation Polymorphism (SSCP) analysis, wherein the analysis comprises comparing a pattern of DNA fragments obtained from the patient DNA sample to a pattern of DNA fragments obtained from a control DNA sample; and

~~(d)~~(f) detecting the presence or absence of said ~~defect~~ truncation, deletion or mutation in the Survival Motor Neuron gene~~, wherein the presence of said defect is indicative of a Survival Motor Neuron disorder~~.

New claims 66-69 have been added.